

EFFICACY STUDY REVIEW

by Kevin J. Sweeney, Entomologist - IB

Kevin J. Sweeney
7/2/03

To: Ann Sibold

Date: July 2, 2000

EPA Registration No. 65331-5

Product Name: Frontline Plus

Registrant: Merial Limited

PM: Marion Johnson, PM 10

Action: 305

Submission No. S630459 DP # : D288661

Chemical: 9.8% fipronil PC Code: 129121

Type: (I) Insecticide RTU spot on dogs & puppies 8 weeks and older

Guideline: OPPTS Product Performance Guideline 810.3300

Data Review Instructions: Review submitted studies and revised label to determine if the product, when use as directed, kills adult mosquitoes.

Submitted Studies:

MRID 45866901 Frontline Plus for Dogs: Study Summaries by Timothy Dotson

A summary of the study below.

MRID 45866902 Frontline Plus for Dogs: A Study to Evaluate the Efficacy of Frontline Plus for Control of Mosquitoes, *Aedes aegypti*, on Dogs by John McCall et al. 2002.

The subject product is applied as a spot-on application to dogs only once per month (every 30 days) in order to kill and control ticks and fleas. If the product is to successful in killing mosquitoes that attack a treated dog, the product should be effective for 30 days. The registrant conducted a study to show that the subject product kills mosquitoes on treated dogs.

1

The study was well organized and had an adequate number of control (untreated) and treated dogs. The mosquito species was the Yellow Fever mosquito, *Aedes aegypti*, a pest species common to the Southeastern United States that prefers mammalian bloodmeals. Frontline Plus applications were made according to the label directions. The study was conducted for 28 days with evaluations at 1, 2, 7, 14, and 28 days post-treatment. At each evaluation, approximately 100 unfed female mosquitoes (range = 47-114) were released into a mosquito-proof cage where a sedated treated/untreated dog resided. The dogs were exposed to the mosquitoes for 30 minutes. At 30 minutes, all dead and live (bloodfed and unfed) mosquitoes were counted. Live mosquitoes were aspirated from the cage into holding cups and mortality was evaluated at 24 and 48 hours. The study director included crushed mosquitoes in the dead mosquito totals (Why? This effect is not treatment related.)

Results were presented for each evaluation date as % mortality at 24 hours and 48 hours post exposure. The Geometric Mean was calculated instead of the Arithmetic Mean to determine mean mortality at each evaluation date and time interval based on (ln) transformed data. The study director concluded that the product was efficacious against mosquitoes for 28 days based on the results of 48 hour post exposure results. However, we usually evaluate product performance data based on 24 hour or less mortality counts. In addition, the product claims to be "Fast-Acting" so we would expect it to kill mosquitoes within 24 hours (preferably by the end of the exposure period) of their exposure to the treatment. If the mosquitoes do not die very quickly -How are dogs protected from mosquitoes?

1. If the raw data on pages 23 and 24 are reviewed and evaluated, the product, based on the results from this experiment, is effective in killing mosquitoes for only seven days. At 14 days, mosquito survivorship is high and mortality is far below 90-95% at 24 hours post-exposure. This result continues for the duration for the study. Results for each evaluation period (and time interval) could have been plotted against time by using the arithmetic mean of the percent effectiveness bracketed by the standard error of that mean in order to more easily visualize the efficacy of the treatment. The control treatments in the present study had very low mortality and correction using Abbott's Formula would have had little impact on the 24 hour mortality results. The variance in percent mortality is not very great either. Applying the Geometric Mean and associated rank analyses to these data did help smooth out the fluctuations in results This evaluation could have plotted in a similar way.

The 48 hour results indicate that the mortality is due to the effect of fipronil treatment. However, this result also indicates that the treatment acts too slowly against mosquitoes to be of any benefit to a treated dog. Mosquito mortality should have been apparent by the end of the 30 minute exposure period.

2. The data support a "kills mosquitoes" claims of 7 days based on the review of the raw data and the 24 hour mortality results reported by the study director based on Geometric Means as well (see summary on page 8 of the MRID...02).

3. It appears that as the concentration of fipronil in dog hair declines or is bound to the hair over time and mosquitoes landing on dogs (including those blood-feeding) do not absorb enough

2

fipronil thru their tarsi/tarsal pads to kill them quickly. This is in contrast to crawling arthropods such as ticks and fleas. Ticks and fleas - by nature of their foraging behavior - stay in contact with the fipronil treated hair and skin over the entire exposure period compared to a landing or biting mosquito. In addition, ticks and fleas probably absorb more fipronil because much of their exoskeleton comes into contact with the treated surfaces. In the case of mosquitoes, it is likely that only the lower leg is exposed and perhaps the proboscis. Mosquitoes are also likely to bite dogs where skin and blood vessels are easily accessed and not in areas where they have to "burrow" or "crawl" thru hair. Fleas and ticks can be found in many areas of the animal although they do tend to favor some areas over others.

4. My only other comment is in regard to the study design. The study director only exposed the mosquitoes to the fipronil treatment for 30 minutes. Many other dog treatment studies accepted by EPA have used a one-hour exposure period and these data have been used to support label claims. I also note that in some of the presentations from the Fourth International Flea and Tick Control Symposium held at the 2003 North American Veterinary Conference reported the results of studies conducted with a one hour exposure period to spot-on treatments to dogs.